Surg Today (2012) 42:613–624
DOI 10.1007/s00595-012-0188-7

REVIEW ARTICLE

Preoperative carbohydrate loading for elective surgery: a systematic review and meta-analysis

Lun Li · Zehao Wang · Xiangji Ying · Jinhui Tian · Tiantian Sun · Kang Yi · Peng Zhang · Zhang Jing · Kehu Yang

Received: 5 August 2011 / Accepted: 13 October 2011 / Published online: 13 May 2012

Abstract
Background and objective It is unclear whether the preoperative administration of oral carbohydrates (CHO) is safe and effective, and therefore we herein evaluated the efficacy and adverse events associated with CHO for elective surgery.
Methods Comprehensive searches were conducted to identify randomized controlled trials (RCTs), which evaluated preoperative CHO for elective surgery. Two reviewers independently selected the trials, extracted data, and assessed the methodological qualities and evidence levels. The data were analyzed by the RevMan 5.0 software program.
Result CHO increased the insulin and glucose levels on the first day after surgery higher than those in overnight fasting group (fifteen RCTs) and i.v. glucose infusion group (three RCTs). The pooled results of thirteen RCTs showed greater declines in the insulin level at the induction of anesthesia and a smaller increase in the glucose level at the end of surgery, and fewer decreases in the postoperative insulin sensitivity index in the CHO group were observed as compared to the placebo group. No aspiration was observed in any of the included studies.
Conclusion CHO appears to be safe, and may attenuate postoperative insulin resistance as compared to placebo. However, the quality of most of the published trials has been poor, and the evidence levels for most outcomes were low, so rigorous and larger RCTs are needed in the future.

L. Li and Z. Wang contributed equally to this paper.

Electronic supplementary material The online version of this article (doi:10.1007/s00595-012-0188-7) contains supplementary material, which is available to authorized users.

L. Li · Z. Wang · X. Ying · J. Tian · K. Yi · P. Zhang · Z. Jing (✉) · K. Yang
Evidence-Based Medicine Center, School of Basic Medical Sciences, Lanzhou University, Dong Gang West Road No. 199, Lanzhou 730000, Gansu, China
e-mail: guo19880101@126.com

L. Li
e-mail: guo19880101@163.com

Z. Wang
e-mail: athlete.dg@gmail.com

X. Ying
e-mail: yingxjii@163.com

J. Tian
e-mail: tjh996@163.com

K. Yi
e-mail: yikang04@126.com

P. Zhang
e-mail: zhp-118@163.com

K. Yang
e-mail: kehuyangebm2006@126.com

L. Li · K. Yi · P. Zhang · K. Yang
The First Clinical College of Lanzhou University, Lanzhou 730000, Gansu, China

Z. Wang · X. Ying
The Second Clinical College of Lanzhou University, Lanzhou 730000, Gansu, China

T. Sun
Shanghai Jiao-Tong University School of Medicine Ren-ji Hospital, Shanghai 20000, China
e-mail: suntt2005@126.com

Z. Jing
Institute of Science and Technology Information of Gansu, Lanzhou 730000, China

Keywords Elective surgical procedure · Carbohydrate loading · Meta-analysis · Systematic review

Introduction

Overnight fasting has long been recommended for elective surgery to ensure that the patient has an empty stomach before anesthesia, which reduces the risk of aspiration [1–6]. However, questions have been recently raised as to whether such fasting is appropriate, especially regarding the fact that overnight fasting depletes the carbohydrate reserves and changes the metabolism, such as the endocrine response (increased glucagon, depleted insulin) and metabolic response (glycogen breakdown, protein breakdown, lipolysis) [4, 6]. Endogenous insulin resistance (IR) is a central feature of the postoperative metabolic response to surgical injury, and might delay the patient recovery after surgery, which could be associated with infectious complications and morbidity [5, 7]. In addition, overnight fasting is uncomfortable (including preoperative thirst, mouth dryness, hunger and anxiety) for surgery patients [2–4]. Therefore, comprehensive perioperative care programs (such as the ERAS protocol) based on the best-available practices in elective surgery were constructed to minimize the metabolic stress of the operation and to support the function of the vital organs [8]. These perioperative care programs have been shown to result in remarkable improvements in both the recovery after surgery and the development of complications [8–10]. In these programs, preoperative carbohydrate (CHO) consumption is an important component that supports both aims, and therefore, is one of the key treatments in the ERAS protocol [8, 11, 12].

Studies have demonstrated that the metabolic responses, including the IR, were significantly attenuated or abolished by the administration of CHO 2 h before elective open general or gastrointestinal surgery, total hip replacement, and thyroidectomy, primarily owing to a decreased reduction in peripheral glucose disposal and increased glucose oxidation rates [2, 13–20]. Preoperative administration of oral CHO could significantly reduce the length of the hospital stay and recovery time as compared with fasting or consumption of a placebo (flavored water) [19, 21]. CHO neither delayed gastric emptying nor affected the gastric acidity [2, 4, 22], and so it was considered to be safe for elective surgical patients [4, 14, 23, 24]. In addition, CHO has been shown to improve preoperative well-being, the postoperative stress hormone response, and prevent surgery-induced immunodepression in patients scheduled for elective general or gastrointestinal surgery [14, 15, 22, 25]. However, some studies showed that preoperative CHO did not shorten the length of hospital stay after major general or gastrointestinal surgery, or improve the IR after elective colorectal, upper-gastrointestinal or coronary artery bypass surgery [18, 25–27].

A traditional review [28] showed that preoperative oral CHO was associated with a shorter length of hospital stay, but another systematic review [29] indicated that statistical significance was not reached for the length of the hospital stay, although trends were seen. The data from these reviews were either outdated or insufficient for health care users. Therefore, we performed a systematic review to evaluate the efficacy and adverse events associated with preoperative CHO for surgical patients.

Methods

We performed this systematic review of the available literature in accordance with the PRISMA guidelines for the conduct of meta-analyses of randomized controlled trials (RCTs).

Search strategy

Systematic, comprehensive literature searches were conducted of PubMed, the Cochrane Library, EMBASE, ISI Web of Knowledge, China Journal Full-text Database, Chinese Biomedical Database, Chinese Scientific Journals Full-text Database, and CMA digital periodicals. All searches were conducted in May 2010, and updated in September 2010, without language or publication status restrictions. The search terms included "preoperative," "carbohydrates," "CHO," "glucose," "fasting," and "surgery". If possible, subject heading terms, such as Medical Subject Headings terms, were added in all searches. Reference lists from relevant review articles were hand-searched. A search of the ClinicalTrials.gov website was also done to identify RCTs, which had been completed but not published. Requests for original data were made by contacting the authors or principal investigators of the studies. All searches were conducted independently by two reviewers (Lun Li and Tiantian Sun); differences were checked by the other investigator and resolved by discussion.

Inclusion criteria and study selection

Randomized controlled trials were eligible for inclusion if they evaluated the preoperative administration of CHO for surgical patients. The comparisons we evaluated were CHO versus overnight fasting, CHO versus placebo (flavored water), and CHO versus i.v. infusion of glucose. Papers that reported at least one outcome that we were interested in, such as the changes in blood glucose and insulin levels (at the induction of anesthesia, at the end of

surgery, on the first day after the operation), the IR index (IRI), the insulin sensitivity index (ISI), gastric pH or volume, the length of hospital or ICU stay, preoperative well-being (anxiety, hunger, thirsty, nausea, or dryness of mouth), postoperative vomiting, and aspiration during surgery, were included. Three reviewers (Zehao Wang, Jinhui Tian, and Kang Yi) independently assessed the potential citations for inclusion, and disagreements were resolved by a fourth reviewer (Kehu Yang).

Data abstraction

Data were abstracted and entered into an Excel database by three authors (Lun Li, Tiantian Sun, and Xiangji Ying). The following fields were extracted: country, patient characteristics (age, sex, etc.), and treatment protocols (details of intervention and comparison(s), sample size, etc.), and outcomes and measured effects. The outcomes were extracted preferentially by the intention-to-treat method. Any disagreements were resolved by a fourth reviewer (Kehu Yang). If data were lacking in the article, we contacted the first author or the corresponding author for further information. If they did not respond within 4 weeks, we extracted as much information as possible from the paper.

Quality and evidence level assessment

The methodological qualities and evidence levels were evaluated by three independent reviewers (Lun Li, Tiantian Sun, and Zehao Wang), and differences were resolved by consultation with a fourth reviewer (Kehu Yang). The following items were assessed according to the Cochrane handbook 5.0 recommended standards [30]: randomization, blinding, concealed allocation, baseline comparability, subject loss to follow-up, intention-to-treat analysis, selective reporting, incomplete outcome data, and other biases. To evaluate the methodological quality for the outcomes evaluated, we used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach [31, 32], which specifies four levels: high, moderate, low, and very low quality evidence.

Data analysis and subgroup analysis

The data were analyzed using the Review Manager Version 5.0 software program. For dichotomous outcomes, the results were expressed as the risk ratio (RR) with the 95 % confidence interval (CI). If there were continuous data, the mean difference (MD), or the standardized mean difference (SMD) if different scales were used, was used to assess the effects of treatment. The data were pooled using the fixed-effects model, but the random-effects model was also considered to ensure the robustness of the model. The percentage of variability across trials attributable to heterogeneity beyond chance was estimated with the I^2 statistic, which was deemed significant for $p < 0.05$ or for $I^2 > 50$ %. In case of significant heterogeneity, the results of the random-effects model were noted. The subgroup analyses were also conducted, for example, using different controls (CHO vs. overnight fasting, CHO vs. placebo, CHO vs. i.v. infusion of glucose) without pooling the overall effects. In addition, the subgroup analyses of different surgeries were conducted, such as for patients undergoing laparoscopic cholecystectomy, colorectal surgery, total hip replacement, cardiac surgery, etc.

Results

Search results

After a comprehensive search, we found 2,605 citations. We excluded 486 duplicates and 1,981 citations based on screening the titles and abstracts. After screening full text articles, we excluded 31 citations (not relevant to CHO), 36 citations (not relevant to surgery), 26 citations (not RCTs), 17 citations (traditional review), and 2 which did not have the outcomes we were interested in investigating [3, 4]. Finally, 22 trials (26 citations) [2, 14, 15, 18, 19, 21, 22, 24–27, 33–47] were included for the analyses (Fig. 1).

Characteristics of included trials

The 22 trials that we analyzed were from Sweden ($n = 6$), China ($n = 4$), Denmark ($n = 2$), the UK ($n = 2$), Finland ($n = 2$), the Czech Republic ($n = 2$), Croatia ($n = 1$), Germany ($n = 1$), Turkey ($n = 1$), and the Netherlands ($n = 1$). They were about colorectal surgery ($n = 7$), cholecystectomy ($n = 3$), orthopedic surgery ($n = 5$), cardiac surgery ($n = 2$), and two or more surgery types ($n = 5$). These studies examined CHO versus placebo ($n = 13$), CHO versus overnight fasting ($n = 15$), and CHO versus glucose (i.v.) ($n = 3$). The timings of CHO administration were 4 h before anesthesia ($n = 1$), the evening before surgery, and 2–3 h before anesthesia ($n = 13$), and 2–3 h before anesthesia ($n = 8$). The number of patients in these trials ranged from 12 to 252. Other information about the trials is presented in Table 1.

Quality assessment

Of these 22 trials, all trials mentioned randomization, 16 trials mentioned blinding, and 12 trials mentioned concealed allocation, but only 10 studies reported the details of randomization, concealed allocation, and blinding. Other information regarding these trials is presented in Table 2.

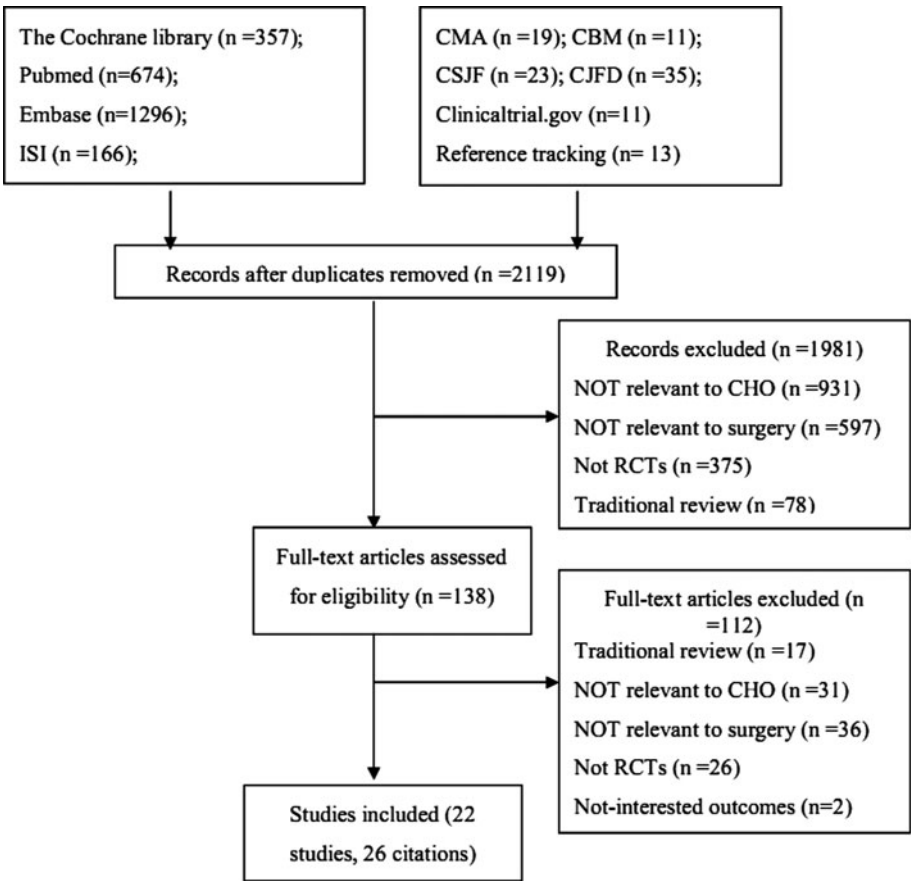

Fig. 1 A flow diagram of the studies

Meta-analysis and systematic review (Supplementary Table 1)

The changes in the insulin level

Greater decreases in the insulin level at the induction of anesthesia in the CHO group were observed than in the placebo group (SMD −0.55, 95 % CI −0.86, −0.24), but statistically significant differences in the changes in the insulin levels at the induction of anesthesia were not observed between the CHO group and the overnight fasting group (SMD −0.53, 95 % CI −1.66, 0.59, $I^2 = 94$ %), or between the CHO group and the i.v. glucose infusion group (SMD −0.29, 95 % CI −0.91, 0.33).

Significant differences in the changes in the insulin levels at the end of surgery were not observed between the CHO and overnight fasting groups (SMD 0.91, 95 % CI −1.55, 3.37, $I^2 = 98$ %), between the CHO and placebo groups (SMD −0.52, 95 % CI −1.31, 0.28, $I^2 = 78$ %), or between the CHO and i.v. glucose infusion groups (SMD 2.00, 95 % CI −0.95, 4.96, $I^2 = 98$ %).

Significantly higher increases in the insulin levels on the first day after surgery in the CHO group were found than those in the overnight fasting group (SMD 0.82, 95 % CI 0.49, 1.16) and the i.v. infusion of glucose group (SMD 0.65, 95 % CI 0.31, 0.98), but no significant difference was observed between the CHO and placebo groups (SMD 0.25, 95 % CI −0.73, 1.23, $I^2 = 91$ %).

The changes in the glucose level

There were no statistically significant differences in the changes in the glucose levels at the induction of anesthesia in these three comparisons: CHO versus overnight fasting (SMD −0.01, 95 % CI −0.64, 0.63, $I^2 = 81$ %), CHO versus placebo (SMD −0.27, 95 % CI −0.70, 0.16, $I^2 = 78$ %), and CHO versus i.v. glucose infusion (SMD 0.22, 95 % CI −0.12, 0.55). Significant differences were also not observed in the changes in the glucose levels at the end of surgery between the CHO and overnight fasting groups (SMD −0.71, 95 % CI −2.44, 1.03, $I^2 = 95$ %), and between the CHO and i.v. glucose infusion groups (SMD −2.23, 95 % CI −4.51, 0.05, $I^2 = 97$ %). However, a smaller increase in the glucose level at the end of surgery in the CHO group was seen than that in the placebo group (SMD −1.47, 95 % CI −2.15, −0.79, $I^2 = 18$ %).

Greater increases in the glucose levels on the first day after surgery were observed in the CHO group than those in the overnight fasting group (SMD 0.77, 95 % CI 0.43, 1.10) and the i.v. infusion of glucose group (SMD 0.79,

Table 1 Characteristics of the included trials

ID	Country	Surgery	Administered dose and time of treatment	*N* (treatment)	Sex (M/F)	Age (years)
Nygren [2]	Sweden	Laparoscopic cholecystectomy/ parathyroid surgery	400 ml CHO[a]/400 ml placebo[a]	6/6	3:3/2:4	46 ± 3/47 ± 7
Hausel [22]	Sweden	Laparoscopic cholecystectomy/ colorectal surgery	800 ml + 400 ml CHO[b]/800 ml + 400 ml placebo[b]/fasting overnight	80/86/86	24:56/34:52/ 23:61	–
Soop [19]	Sweden	Total hip replacement	800 + 400 ml CHO[b]/800 + 400 ml placebo[b]	8/7	1:7/3:4	66 ± 3/58 ± 3
Henriksen [43]	Denmark	Bowel resections	400 ml + 400 ml CHO[b]/400 ml + 400 ml placebo[b]	17/16	6:11/8:8	64/64
Soop [44]	Sweden	Total hip replacement	800 + 400 ml CHO[b]/800 + 400 ml placebo[b]	8/6	3:5/6:0	59/66
Bisgaard [45]	Denmark	Laparoscopic cholecystectomy	800 + 400 ml CHO[b]/800 + 400 ml placebo[b]	43/43	6:37/9:34	42/44
Pu [40]	China	Orthopedic surgery	CHO 10 ml/kg[c]/800 ml 5 % glucose solution (i.v.)[a]/fasting overnight	20/20/20	–	–
Hausel [33]	Sweden	Laparoscopic cholecystectomy	800 + 400 ml CHO[b]/800 + 400 ml placebo[b]/fasting overnight	55/59/58	41: 14/41: 18/45: 13	48.3 ± 14.6/46.8 ± 14.9/ 48.0 ± 14.9
Yuill [18]	UK	Elective abdominal surgery	800 ml + 400 ml CHO[b]/800 ml + 400 ml placebo[b]	31/34	20:11/19:15	52.8 ± 2.5/52.1 ± 2.4
Melis [14]	The Netherlands	Elective orthopedic surgery	400 ml CHO[c]/fasting overnight	20/10	13:7/2:7	–
Noblett [21]	UK	Colorectal resections	800 ml + 400 ml CHO[b]/800 ml + 400 ml placebo[b]/fasting overnight	10/11/12	–	58/59/55
Breuer [38]	Germany	Elective cardiac surgery	800 ml + 400 ml CHO[b]/800 ml + 400 ml placebo[b]/fasting overnight	56/60/44	15:41/10:50/ 10:34	64 ± 9/64 ± 10/64 ± 10
Helminen [34]	Finland	General or gastrointestinal surgery	1000 ml 5 % glucose solution (i.v.) overnight/400 ml CHO[c]/ fasting overnight	67/70/73	25:42/26:44/ 22:51	61 ± 16/60 ± 15/58 ± 4
Järvelä [27]	Finland	Coronary artery bypass grafting surgery	400 ml CHO[c]/fasting overnight	50/51	11:39/6:45	64.0 ± 8.6/66.8 ± 11.4
An [35, 36]	China	Colorectal resection	50 g CHO[c]/fasting overnight	27/24	14:13/12:12	–
Aronsson [46]	Sweden	Total hip replacement	800 + 200 ml CHO[b]/800 + 200 ml placebo[b]	15/14	4:10/6:9	69/66
Yagci [24]	Turkey	Laparoscopic cholecystectomy/ thyroidectomy	800 ml + 400 ml CHO[b]/fasting overnight	34/36	14:20/15:21	49.59 ± 15.2/43.11 ± 15.1
Faria [37]	Czech Republic	Laparoscopic cholecystectomy	200 ml CHO[c]/fasting overnight	12/13	0:11/0:10	47/48
Kaška [39]	Czech Republic	Colorectal surgery	500 ml 10 % glucose solution (i.v.) overnight and the morning 2–6 h before surgery/400 ml + 400 ml CHO[b]/fasting overnight	72/74/75	–	60.4

Table 1 continued

ID	Country	Surgery	Administered dose and time of treatment	*N* (treatment)	Sex (M/F)	Age (years)
Mathur [25, 26]	New Zealand	Colorectal surgery/ hepatic resection	800 ml + 400 ml CHO[b]/800 ml + 400 ml placebo[b]	69/73	29:40/44:29	60/65
Wang [15, 41, 42]	China	Colorectal cancer resection	400 ml CHO[c]/400 ml placebo[c]/fasting overnight	16/16/16	11:5/8:8/9:7	66/62/63
Yang [47]	China	Colorectal cancer resection	250 ml CHO[c]/250 ml placebo[c]/fasting overnight	30/30/30	13:17/11:19/ 8:22	55 ± 14.2/57 ± 12.4/58 ± 14.5

Placebo flavored water, *M* mentioned, *U* unclear

[a] Time: 4 h before anesthesia

[b] Time: first, the evening before surgery; second 2–3 h before anesthesia; (the dose before the "+" was the first dose administered, and the dose after the "+" was the second dose administered)

[c] Time: 2–3 h before anesthesia

95 % CI 0.50, 1.08, $I^2 = 0$ %), but there was no statistically significant difference in the glucose levels on the first day after the surgery between the CHO and placebo groups (SMD 0.04, 95 % CI −0.28, 0.36).

Postoperative ISI and IRI

A significant difference in the change in the ISI was seen between the CHO and placebo groups (SMD 1.06, 95 % CI 0.32, 1.81), but there were no significant differences in the other two comparisons: CHO versus overnight fasting (SMD 0.34, 95 % CI −0.73, 1.40, $I^2 = 93$ %), CHO versus i.v. glucose infusion (SMD −0.46, 95 % CI −1.14, 0.21, $I^2 = 72$ %). There were also no significant differences in the changes in the postoperative IRI between the CHO and overnight fasting groups (SMD −1.02, 95 % CI −2.60, 0.56, $I^2 = 86$ %) or between the CHO and placebo groups (SMD −0.61, 95 % CI −1.96, 0.75, $I^2 = 90$ %).

Length of hospital stay and ICU stay

The length of the hospital stay in the CHO group tended to be longer than that in i.v. infusion glucose group (SMD 0.45, 95 % CI 0.12, 0.78), but there were no significant differences between the CHO and overnight fasting groups (SMD −0.06, 95 % CI −0.49, 0.37, $I^2 = 65$ %) or between the CHO and placebo groups (SMD −0.32, 95 % CI −0.81, 0.17, $I^2 = 77$ %).

There were also not any statistically significant differences in the length of ICU stay between the CHO and overnight fasting groups (SMD −0.15, 95 % CI −0.44, 0.14, $I^2 = 7$ %) or between the CHO and placebo groups (SMD 0.22, 95 % CI −0.14, 0.59).

Postoperative gastric pH and residue volume

The gastric pH was not significantly different between the CHO and overnight fasting groups (SMD 0.01, 95 % CI −0.35, 0.36, $I^2 = 56$ %) or between the CHO and placebo groups (SMD −0.08, 95 % CI −0.37, 0.20, $I^2 = 12$ %).

There were no significant differences in the gastric residual volume between the CHO and overnight fasting groups (SMD −0.11, 95 % CI −0.36, 0.15, $I^2 = 19$ %) or between the CHO and placebo groups (SMD −0.03, 95 % CI −0.30, 0.24, $I^2 = 4$ %).

Postoperative vomiting and aspiration during surgery

There were no significant differences in the incidence of postoperative vomiting between the CHO and overnight fasting groups (RR 0.90, 95 % CI 0.47, 1.72) or between the CHO and placebo groups (RR 1.31, 95 % CI 0.23, 7.45). Six trials [14, 15, 18, 22, 38, 41, 42, 45] mentioned

Table 2 Quality assessment of the included studies

ID	Randomization	Blinding	Allocation concealed	Eligibility criteria	Baseline comparability	≥80 % participants followed up	ITT analysis	Selective reporting	Incomplete outcome data	Other biases
Nygren [2]	M	U	U	Y	Y	Y	Y	U	N	U
Hausel [21]	M	M, double-blinded	U	Y	Y	Y	Y	U	U	U
Soop [19]	Y	M	U	Y	Y	Y	Y	U	U	U
Henriksen [43]	Y	Blinded to investigators	Y	Y	Y	Y	U	U	N	U
Soop [44]	Y	M	U	Y	Y	Y	U	U	U	U
Bisgaard [45]	Y	Blinded to patients, surgeons, investigators	Y	Y	Y	Y	U	U	U	U
Pu [40]	M	U	U	Y	Y	Y	Y	U	U	U
Hausel [33]	Y	Blinded to patients, investigators	Y	Y	Y	Y	Y	U	U	U
Yuill [18]	M	U	U	Y	Y	Y	N	U	U	U
Melis [14]	M	Blinded to investigators and patients	Y	Y	U	Y	Y	U	U	U
Noblett [22]	Y	Blinded to surgeons	Y	Y	Y	Y	Y	U	U	U
Breuer [38]	Y	Blinded to patients, surgeons, investigators	Y	Y	Y	Y	Y	U	U	U
Helminen [34]	M	U	Y	Y	Y	Y	Y	U	N	U
Järvelä [27]	M	Blinded to surgeons	Y	Y	U	Y	U	U	N	U
An [35, 36]	M	U	U	Y	Y	Y	Y	U	N	U
Aronsson [46]	M	M	U	Y	Y	Y	Y	U	N	U
Yagci [24]	M	Blinded to investigators	U	Y	Y	Y	Y	U	U	U
Faria [37]	Y	U	Y	Y	Y	Y	Y	U	U	U
Kaška [39]	M	M	Y	Y	N	N	Y	U	U	U
Mathur [25, 26]	Y	Blinded to patients, investigators	Y	Y	Y	Y	U	U	U	U
Wang [15, 41, 42]	M	Blinded to patients, investigators	Y	Y	Y	Y	Y	U	N	U
Yang [47]	Y	M	U	Y	Y	Y	Y	U	U	U

M mentioned (the study just mentioned randomization or blinding, but it did not described the detailed methods), *Y* yes (the study mentioned randomization or blinding, and it described the detailed methods), *U* unclear

aspiration, and none of them reported any incidents of either vomiting or aspiration (CHO vs. overnight fasting, CHO vs. placebo).

Preoperative well-being

The results regarding preoperative hunger and anxiety were inconsistent for the comparisons between the CHO and overnight fasting groups and between the CHO and placebo groups. Less thirst was observed in the CHO group than that in the overnight fasting group. However, the results about thirst between the CHO group and placebo group were contradictory. No statistically significant differences were found in the rates of nausea and dry mouth between the CHO group and the overnight fasting group or between the CHO group and the placebo group (Supplementary Table 2).

Results of the subgroup analysis of patients undergoing different surgeries

Colorectal surgery (Supplementary Table 3)

Seven RCTs [15, 21, 22, 35, 36, 39, 41–43, 47] supplied enough data to evaluate the effect of CHO on patients undergoing colorectal surgery. In the comparison of CHO with overnight fasting, statistically significant differences were only observed in the insulin level on the first day after surgery (SMD 0.82, 95 % CI 0.49, 1.16), the glucose level on the first day after surgery (SMD 0.77, 95 % CI 0.43, 1.10), the ISI (SMD −0.38, 95 % CI −0.65, −0.11, $I^2 = 94$ %), and the IRI (SMD −1.82, 95 % CI −2.67, −0.98). However, there were no significant differences in any other outcomes (insulin and glucose levels at the end of surgery, the length of hospital stay, gastric volume, or gastric pH). Less hunger, anxiety, and thirst were observed in both RCTs [15, 39, 41, 42], but preoperative nausea was not reduced [15, 41, 42].

In the comparison of CHO with placebo, a smaller increase in the insulin level (SMD −1.35, 95 % CI −2.12, −0.57) and glucose level (SMD −1.06, 95 % CI −1.81, −0.31) at the end of surgery, a smaller decrease in the ISI (SMD 1.06, 95 % CI 0.32, 1.81) and a smaller increase in the IRI (SMD −1.34, 95 % CI −2.12, −0.57) were seen. However, there were no significant differences in any other outcomes (the length of hospital stay, gastric volume, and gastric pH). CHO could not reduce the preoperative anxiety and nausea in one RCT [43]; however, the results for preoperative thirst were inconsistent in the two RCTs [15, 41–43].

In the comparison of CHO with i.v. infusion glucose, a greater increase in the insulin levels at the end of surgery (SMD 3.51, 95 % CI 2.99, 4.03) and on the first day after surgery (SMD 0.65, 95 % CI 0.31, 0.98) and a longer hospital stay (SMD 0.45, 95 % CI 0.12, 0.78) were observed. However, no significant differences in the other outcomes (insulin and glucose levels at the induction of anesthesia, glucose level at the end of surgery, ISI) were seen.

Laparoscopic cholecystectomy (Supplementary Table 4)

Three RCTs [22, 33, 37] supplied enough data about laparoscopic cholecystectomy for an analysis. However, there were no significant differences in the insulin level at the end of surgery, the IRI, gastric volume, gastric pH, or vomiting in the comparison of CHO with overnight fasting, in the gastric volume, gastric pH and vomiting in the comparison of CHO with placebo, or in the glucose level at the end of surgery in the comparison of CHO with i.v. infusion glucose. Two RCTs [33, 45] reported that CHO could not reduce the preoperative hunger any better than overnight fasting, and could not decrease nausea better than the placebo.

Total hip replacement (Supplementary Table 5)

Three RCTs [19, 44, 46] supplied enough data for an analysis of subjects undergoing total hip replacement. A smaller increase in the glucose level at the end of surgery (SMD −1.98, 95 % CI −2.92, −1.03) was observed in the comparison of CHO with placebo. However, there were not any statistically significant differences in the other outcomes (insulin level at the end of surgery or glucose levels at the induction of anesthesia).

Cardiac surgery

Two RCTs [27, 38] supplied enough data about cardiac surgery for an analysis. However, there were no significant differences in the glucose levels at the induction of anesthesia, or the length of the hospital and ICU stays when CHO was compared with overnight fasting or placebo, nor were there any differences in the incidence of vomiting when CHO was compared with overnight fasting. There were no significant differences in preoperative hunger, nausea, or mouth dryness in the comparisons of CHO with placebo or overnight fasting. Less thirst was observed in the comparison of CHO with overnight fasting [38].

Evidence level assessment

We evaluated the quality of the evidence of the outcomes except for the preoperative well-being. The quality of evidence for aspiration was low, as some important methodological items of the included studies were inadequate, and the sample size of the included studies was

small. In the remaining 34 outcomes, only 4 outcomes achieved a moderate evidence level; 13 outcomes had very low quality of the evidence, and the remaining 18 outcomes had a low quality of evidence (Supplementary Table 1).

Discussion

Evidence summary

The present meta-analysis of 13 trials comparing CHO with placebo showed that greater decreases in the insulin level at the induction of anesthesia and smaller increases in the glucose level at the end of surgery were observed in the CHO group than those in the placebo group. Fewer decreases in the postoperative ISI were observed in the CHO group than that in the placebo group. This indicated that CHO may attenuate the immediate postoperative IR as compared to the placebo. However, the number of included studies was too small to draw a definitive conclusion. In addition, the quality of the evidence for most outcomes was relatively low, so further research is likely to have an impact on our confidence in the estimate of the effects of CHO.

The meta-analysis of 15 trials comparing CHO with overnight fasting showed that CHO increased the insulin and glucose levels on the first day after surgery more than the levels observed in the overnight fasting group. However, our results were inconsistent with the results of a primary study [39], as the baseline insulin levels between the CHO and overnight fasting groups differed. In addition, only one study with 149 patients was evaluated for this outcome, and the quality of evidence for these two outcomes was low. As a result, the differences from the available evidence were not affirmative.

The meta-analysis of the three trials of CHO as compared to i.v. glucose infusion showed that there were increased insulin and glucose levels on the first day after surgery and a longer hospital stay in the CHO group than those in the i.v. glucose infusion group. However, the baseline insulin levels differed between the CHO and i.v. glucose infusion groups in the previously published study [39]. Moreover, the numbers of included studies were small for these two outcomes, and the quality of the evidence for these two outcomes was low, so we were not confident about the results.

With regard to the patients' preoperative well-being, CHO could reduce preoperative thirst as compared to overnight fasting, but not as compared to placebo. However, CHO could not decrease the incidence of preoperative nausea or mouth dryness as compared to either overnight fasting or placebo. In terms of the preoperative hunger and anxiety, the results of the included studies were inconsistent. However, the data about the preoperative patient well-being, from the included studies, were not pooled to produce a more conclusive result, as the data from all relevant studies were not presented in a format that allowed pooling. Nevertheless, the available evidence suggested that the preoperative well-being might be improved after CHO intake to at least some degree.

No aspiration was observed in any of the studies that reported this outcome. The incidence of postoperative vomiting was not significantly different between the CHO and overnight fasting groups, or between the CHO and placebo groups, which meant that CHO was safe based on the available evidence. However, the sample sizes of the included studies were not large enough, and the quality of evidence was low, so caution must be exercised when CHO is used.

Among the outcomes we evaluated, CHO did not show better benefits in patients undergoing laparoscopic cholecystectomy as compared to overnight fasting, placebo, or i.v. infusion of glucose, or in patients undergoing cardiac surgery as compared to overnight fasting or placebo (except that less thirst was observed in the comparison of CHO with overnight fasting). A smaller increase in the glucose levels at the end of surgery was observed in the comparison of CHO with placebo in patients undergoing total hip replacement. For those undergoing colorectal surgery, a greater increase in the insulin and glucose levels on the first day after surgery and the glucose levels at the induction of anesthesia, as well as less IRI, hunger, anxiety, and thirst were observed in the comparison of CHO with overnight fasting. A smaller increase in the insulin and glucose levels at the end of surgery, a smaller decrease in the ISI, and a lower increase in the IRI were seen in the comparison of CHO with placebo. A greater increase in the insulin levels at the end of surgery and on the first day after surgery, and a longer hospital stay, were observed in the comparison of CHO with i.v. infusion glucose.

Overall, the 15 trials comparing CHO with overnight fasting showed that CHO increased the insulin and glucose levels on the first day after surgery as compared to the overnight fasting group, and with less preoperative thirst. Thirteen trials comparing CHO with placebo showed that greater decreases in the insulin level at the induction of anesthesia and a smaller increase in the glucose level at the end of surgery were found in the CHO group as compared to the placebo group. Fewer decreases in the postoperative ISI were observed in the CHO group than in the placebo group. In addition, CHO was associated with more increased insulin and glucose levels on the first day after surgery and a longer hospital stay than were noted in the i.v. glucose infusion group. No aspiration was observed in any of the included studies.

With regard to the different types of surgeries, the effects of CHO were different. CHO seemed to decrease the IRI as compared to overnight fasting, as well as increasing the ISI and decreasing the IRI as compared to placebo treatment in patients undergoing colorectal surgery. No significant effects were observed for any of the other surgeries evaluated. However, the number of studies included for the analysis of each type of surgery was limited, so we could not draw definitive conclusions.

In addition, the heterogeneity across the included studies was significant. There were likely two main reasons for this: first, the administration dose or timing of CHO was not the same across the included studies. There were two different administration methods: once or twice before surgery. The administration timings of the two doses of CHO protocol were the evening before surgery (first) and 2–4 h before anesthesia (second), while the administration time for the single CHO protocol was 2–4 h before anesthesia. These different numbers and times of CHO could be one source of the high heterogeneity. Second, many different types of surgery were performed. The types of surgery included laparoscopic cholecystectomy, colorectal surgery, total hip replacement, cardiac surgery, etc. Although we conducted the subgroup analyses and calculated the changes in the outcomes after the intake of CHO between two groups, heterogeneity still existed. As a result, the different surgeries could be another source of the high heterogeneity. Therefore, there was a high degree of inconsistency in the results, and when our results are applied to clinical practice, additional attention should be paid, and patients should be treated cautiously.

Study quality and evidence levels

The available evidence showed that inadequate random allocation or concealed allocation would result in overestimates of the effect [48]. However, 10 of the 22 included trials reported the details of randomization, concealed allocation, and blinding. It is well known that the subjective outcomes or patient-reported outcomes need to be blinded to patients, as a lack of blinding in randomized trials can be associated with more exaggerated estimated intervention effects [30, 49, 50]. However, the assessment of the blinding of these nine studies [2, 14, 15, 22, 33, 34, 38, 39, 41–43, 45], which reported preoperative well-being, was not satisfactory. Six of the nine studies mentioned blinding, but only five of the nine were blinded to patients. The overall quality of these trials focusing on CHO for elective surgery were poor, and the pooled results of these trials need to be cautiously interpreted when applying them to clinical practice.

The number of patients included for each outcome was small, and inconsistencies existed across trials, so a high level of evidence was not produced by these trials. As a result, it is necessary to be prudent about using the results from these studies to recommend new strategies for clinical practice.

Study limitations

Our present study aimed to overview the efficacy and side effects of CHO for elective surgery, so we searched all RCTs that compared CHO with overnight fasting, placebo or i.v. glucose. This is the first article about this topic that performed a comprehensive search of all of the relevant medical electronic databases and ClinicalTrials.gov, and that tracked reference lists from review articles, and where the authors of the original articles were contacted. Three of our authors independently screened all of the trials, extracted data, and assessed the methodological quality and quality of evidence in order to avoid selection and performance biases.

Nevertheless, this paper still has several limitations. First, we just searched Chinese and English databases, while the databases in other languages were not searched, so studies that were published in other languages could not be included. Second, we did not consider the administration time, dose and amount of CHO, although these may influence gastric emptying. Therefore, the heterogeneity of the pooled results was high for each outcome. Third, a possible criticism of this systematic review is that it was based on trials of small sample sizes, and almost none of them reported sample calculations. Therefore, in the future, a sample calculation should be conducted before beginning a RCT to make it possible to achieve a sufficiently powerful analysis.

Implications for practice and research

A traditional review, which was published in 2009 [9], summarized the present understanding of the mechanisms underlying the positive clinical effects and finally stated that preoperative CHO loading was recommended before a major surgery. Despite the fact that preoperative CHO has some positive effects and has even been recommended in several countries, preoperative overnight fasting is still the standard of care in many hospitals [14]. This is because most patients and clinicians are afraid of the increased risk of aspiration. The results from our meta-analysis showed that no incidents of aspiration were observed in the six reports [14, 15, 18, 22, 38, 41, 42, 45] that mentioned aspiration. This is consistent with the results of a Cochrane systematic review [23], which showed that a shortened fluid fast was not associated with an increased risk of aspiration as compared with the standard "nil by mouth from midnight" fasting policy. However, the quality of the

evidence for this outcome was low, as some important methodological items were inadequate, and the sample size was too small to accurately judge whether aspiration will occur when the sample size is increased or when the method is applied to more patients. Preoperative oral consumption of 800 ml of a carbohydrate-rich drink the evening before surgery, and 400 ml 2 h before anesthesia for elective surgery was recommended in the UK [51], and also in Germany [52], and in Scandinavia [53] during the past several years, but preoperative oral CHO for elective surgery did not appear to provide any major benefit based on the results of our present systematic review. Our study demonstrated that CHO might attenuate the postoperative IR as compared to placebo, and for colorectal surgery, the postoperative IR was decreased for the CHO group as compared with patients who were treated following overnight fasting or the administration of a placebo. However, the recommendations for applying these results in practice should be made cautiously, as poor methodological quality and a low quality of evidence were generally present for these studies. In addition, clinicians should keep in mind that preoperative oral CHO could not be used in patients with a hiatus hernia, known upper gastrointestinal tumor, slow gastric emptying, or diabetes [12].

The number of patients included in these trials was very small. Although a difference in treatment can be seen with a small sample (but with sufficient power analysis), we believe that samples should be large enough to detect possible differences, reasonable enough to be feasible, and small enough to detect efficient therapies [37, 54]. The methodological quality of the included trials was not good enough, which may have introduced some potential bias into the pooled results. Therefore, further RCTs should be designed using more rigorous methods to avoid potential biases and make the evidence more reliable.

Conclusion

Carbohydrates may be safe and attenuate postoperative insulin resistance better than placebo. However, the quality of the trials included in this analysis was poor, and the evidence levels for most outcomes were low. Therefore, caution should be exercised when applying these results for clinical practice. In addition, further, better-designed RCTs should be performed with rigorous methods to avoid potential biases and to make the evidence more reliable.

Acknowledgments This research was funded by the academic Newcomer Award for Ph.D of Lanzhou University, but the foundation did not play any role in conducting the research, including interpreting the results.

Conflict of interest None.

References

1. Lister J. On anaesthetics, part III. In: Holmes' system of surgery, vol. III. 3rd ed. London; 1883. p. 135-175 (reprinted in: The Collected Papers of Joseph Lister Birmingham: Leslie B. Adams Jr. Classics of Medicine Library 1979).
2. Nygren J, Thorell A, Jacobsson H, Larsson S, Schnell PO, Hylén L, et al. Preoperative gastric emptying. Effects of anxiety and oral carbohydrate administration. Ann Surg. 1995;222:728–34.
3. Nygren J, Soop M, Thorell A, SreeNair K, Ljungqvist O. Preoperative oral carbohydrates and postoperative insulin resistance. Clin Nutr. 1999;18:117–20.
4. Protic A, Turina D, Matani D, Spanjol J, Zuvic-Butorac M, Sustic A. Effect of preoperative feeding on gastric emptying following spinal anesthesia: a randomized controlled trial. Wien Klin Wochenschr. 2010;122:50–3.
5. Ljungqvist O, Nygren J, Hausel J, Thorell A. Preoperative nutrition therapy-novel developments. Food Nutr Res. 2000;44:3–7.
6. Thorell A, Nygren J, Ljungqvist O. Insulin resistance: a marker of surgical stress. Curr Opin Clin Nutr Metab Care. 1999;2:69–78.
7. Mendelson CL. The aspiration of stomach contents into the lungs during obstetric anesthesia. Obstet Gynecol Surv. 1946;1:837–9.
8. Muller S, Zalunardo MP, Hubner M, Clavien PA, Zurich Fast Track Study Group. A fast-track program reduces complications and length of hospital stay after open colonic surgery. Gastroenterology. 2009;136:842–7.
9. Ljungqvist O. Modulating postoperative insulin resistance by preoperative carbohydrate loading. Best Pract Res Clin Anaesthesiol. 2009;23:401–9.
10. Fearon KC, Ljungqvist O, Von Meyenfeldt M, Revhaug A, Dejong CH, Lassen K, Nygren J, et al. Enhanced recovery after surgery: a consensus review of clinical care for patients undergoing colonic resection. Clin Nutr. 2005;24:466–77.
11. Eskicioglu C, Forbes SS, Aarts MA, Okrainec A, McLeod RS. Enhanced recovery after surgery (ERAS) programs for patients having colorectal surgery: a meta-analysis of randomized trials. J Gastrointest Surg. 2009;13:2321–9.
12. Søreide E, Ljungqvist O. Modern preoperative fasting guidelines: a summary of the present recommendations and remaining questions. Best Pract Res Clin Anaesthesiol. 2006;20:483–91.
13. Lauwick SM, Kaba A, Maweja S, Hamoir EE, Joris JL. Effects of oral preoperative carbohydrate on early postoperative outcome after thyroidectomy. Acta Anaesthesiol Belg. 2009;60:67–73.
14. Melis GC, van Leeuwen PAM, der vonBlomberg-van B, Mary E, Goedhart-Hiddinga AC, Uitdehaag BMJ, et al. A carbohydrate-rich beverage prior to surgery prevents surgery-induced immunodepression: a randomized, controlled, clinical trial. J Parenter Enter Nutr. 2006;30:21.
15. Wang Z, Wang Q, Wang W, Qin H. Randomized clinical trial to compare the effects of preoperative oral carbohydrate versus placebo on insulin resistance after colorectal surgery. Br J Surg. 2010;97:317–27.
16. Ljungqvist O, Nygren J, Thorell A. Modulation of post-operative insulin resistance by pre-operative carbohydrate loading. Proc Nutr Soc. 2002;61:329–36.
17. Nygren J, Soop M, Thorell A, SreeNair K, Ljungqvist O. Preoperative oral carbohydrates and postoperative insulin resistance. Clin Nutr. 1999;18:117–20.
18. Yuill KA, Richardson RA, Davidson HIM, Garden OJ, Parks RW. The administration of an oral carbohydrate-containing fluid prior to major elective upper-gastrointestinal surgery preserves skeletal muscle mass postoperatively—a randomised clinical trial. Clin Nutr. 2005;24:32–7.
19. Soop M, Nygren J, Myrenfors P, Thorell A, Ljungqvist O. Preoperative oral carbohydrate treatment attenuates immediate

postoperative insulin resistance. Am J Physiol Endocrinol Metab. 2001:E576–583.
20. Nygren J, Soop M, Thorell A, Efendic S, Nair K, Ljungqvist O. Preoperative oral carbohydrate administration reduces postoperative insulin resistance. Clin Nutr. 1998;17:65–71.
21. Noblett SE, Watson DS, Huong H, Davison B, Hainsworth PJ, Horgan AF. Pre-operative oral carbohydrate loading in colorectal surgery: a randomized controlled trial. Colorect Dis Off J Assoc Coloproctol Great Britain Ireland. 2006:563–9.
22. Hausel J, Nygren J, Lagerkranser M, Hellström PM, Hammarqvist F, Almstrm C, et al. A carbohydrate-rich drink reduces preoperative discomfort in elective surgery patients. Anesth Analg. 2001;93:1344–50.
23. Brady M, Kinn S, Stuart P. Preoperative fasting for adults to prevent perioperative complications. Cochr Database Syst Rev (online). 2003.
24. Yagci G, Can M, Ozturk E, Dag B, Ozgurtas T, Cosar A, et al. Effects of preoperative carbohydrate loading on glucose metabolism and gastric contents in patients undergoing moderate surgery: a randomized, controlled trial. Nutrition (Burbank, Los Angeles County, Calif). 2008;24:212–6.
25. Mathur S, Shapkov P, McIlroy K, Gillanders L, Plank LD. Preoperative carbohydrate loading in patients undergoing major general or gastrointestinal surgery: results of a double-blind randomised controlled trial. Nutrition. 2008;24:511–2 (selected abstracts).
26. Mathur S, Plank LD, McCall JL, Shapkov P, McIlroy K, Gillanders LK, et al. Randomized controlled trial of preoperative oral carbohydrate treatment in major abdominal surgery. Br J Surg. 2010;97:485–94.
27. Järvelä K, Maaranen P, Sisto T. Pre-operative oral carbohydrate treatment before coronary artery bypass surgery. Acta Anaesthesiol Scand. 2008;52:793–7.
28. Ljungqvist O, Nygren J, Thorell A, Brodin U, Efendic S. Preoperative nutrition—elective surgery in the fed or the overnight fasted state. Clin Nutr. 2001;20:167–71.
29. Shanley S. Preoperative carbohydrate loading: a review of the current evidence. J Hum Nutr Diet. 2009;22:261–2.
30. Higgins JPT, Green S. Cochrane Handbook for systematic reviews of interventions version 5.0.2 (updated September 2009). The Cochrane Collaboration. http://www.Cochrane-handbook.org.
31. Schunemann HJ, Jaeschke R, Cook DJ, Bria WF, El-Solh AA, Ernst A, et al. An official ATS statement: grading the quality of evidence and strength of recommendations in ATS guidelines and recommendations. Am J Respir Crit Care Med. 2006;174:605–14.
32. Akl E, Muti P, Sch nemann H. Anticoagulation in patients with cancer: an overview of reviews. Polskie Archiwum Medycyny Wewn (tm) trznej. 2008;118:183.
33. Hausel J, Nygren J, Thorell A, Lagerkranser M, Ljungqvist O. Randomized clinical trial of the effects of oral preoperative carbohydrates on postoperative nausea and vomiting after laparoscopic cholecystectomy. Br J Surg. 2005:415–21.
34. Helminen H, Viitanen H, Sajanti J: Effect of preoperative intravenous carbohydrate loading on preoperative discomfort in elective surgery patients. Eur J Anaesthesiol. 2009:123–7.
35. An GQ, Zhao XL, Gao YC, Wang GY, Yu YM. Effects of preoperative carbohydrate loading on the changes in serum tumor necrosis factor receptors 1 and 2 and insulin resistance in patients of colon carcinoma. Zhonghua Yi Xue Za Zhi. 2008;88:2041–4.
36. An GQ, Zhao XL, Gao YC, Wang GY, Yu YM. The effects of preoperative carbohydrate loading on the changes in sTNFR1, sTNFR2 and insulin resistance in patients with colon carcinoma. Hebei Med J. 2008;30:618–20.
37. Faria MSM, de Aguilar-Nascimento JE, Pimenta OS, Alvarenga LC, Dock-Nascimento DB, Slhessarenko N. Preoperative fasting of 2 hours minimizes insulin resistance and organic response to trauma after video-cholecystectomy: a randomized, controlled, clinical trial. World J Surg. 2009;33:1158–64.
38. Breuer JP, von Dossow V, von Heymann C, Griesbach M, von Schickfus M, Mackh E, et al. Preoperative oral carbohydrate administration to ASA III–IV patients undergoing elective cardiac surgery. Anesth Anal. 2006:1099–108.
39. Kaska M, Grosmanová T, Havel E, Hypler R, Petrová Z, Brtko M, et al. The impact and safety of preoperative oral or intravenous carbohydrate administration versus fasting in colorectal surgery-a randomized controlled trial. Wien Klin Wochenschr. 2010;122:23–30.
40. Pu XL, Sun CZ, Li L, Zeng X, Wang WH. Effect of preoperative carbohydrate supplementation on insulin resistance in patients after scar ectomy. J Reg Anat Oper Surg. 2005;14:368–70.
41. Wang ZG, Yang Z, HL Q. Study of mechanism of preoperative oral carbohydrate involved in attenuating postoperative insulin resistance. Chin J Bases Clin Gen Surg. 2008;15:799–804.
42. Wang ZG, Yang Z, HL Q. The effect of the preoperative oral carbohydrate treatment on immediate postoperative insulin resistance in patients after colorectal cancer resection. Parenter Enter Nutr. 2008;15:339–42.
43. Henriksen MG, Hessov I, Dela F, Hansen HV, Haraldsted V, Rodt SA: Effects of preoperative oral carbohydrates and peptides on postoperative endocrine response, mobilization, nutrition and muscle function in abdominal surgery. Acta Anaesthesiol Scand. 2003:191–9.
44. Soop M, Nygren J, Thorell A, Weidenhielm L, Lundberg M, Hammarqvist F, et al. Preoperative oral carbohydrate treatment attenuates endogenous glucose release 3 days after surgery. Clin Nutr (Edinburgh, Scotland). 2004:733–41.
45. Bisgaard T, Kristiansen V, Hjorts N, Jacobsen L, Rosenberg J, Kehlet H. Randomized clinical trial comparing an oral carbohydrate beverage with placebo before laparoscopic cholecystectomy. Br J Surg. 2004;91:151–8.
46. Aronsson A, Al-Ani NA, Brismar K, Hedstrom M. A carbohydrate-rich drink shortly before surgery affected IGF-I bioavailability after a total hip replacement. A double-blind placebo controlled study on 29 patients. Aging Clin Exp Res. 2009;21:97–101.
47. Yang DJ, He YL, Cai SR, Zhang CH, Wu H, Peng JJ, et al. Effects of drinking fluid hours before anesthesia on gastric fluid volume and pH in patients with colorectal cancer. J Dig Oncol. 2009;1:46–9.
48. Kunz R, Vist G, Oxman A. Randomisation to protect against selection bias in healthcare trials. Cochrane Database Syst Rev. 2007; Art no MR000012.
49. Pildal J, Hrobjartsson A, Jrgensen K, Hilden J, Altman D, Gtzsche P. Impact of allocation concealment on conclusions drawn from meta-analyses of randomized trials. Int J Epidemiol. 2007;36:847.
50. Wood L, Egger M, Gluud LL, Schulz KF, Jüni P, Altman DG, et al. Empirical evidence of bias in treatment effect estimates in controlled trials with different interventions and outcomes: meta-epidemiological study. bmj 2008; 336: 601.
51. Powell-Tuck J, Gosling P, Lobo D, Allison S, Carlson G, Gore M. British consensus guidelines on intravenous fluid therapy for adult surgical patients (GIFTASUP). London: NHS National Library of Health. http://wwwicsacuk/downloads/2008112340_GIFTASUP%20FINAL_31-10-08 pdf (accessed 11 January 2009).
52. Spies C, Breuer J, Gust R, Wichmann M, Adolph M, Senkal M, et al. Preoperative fasting. An update. Der Anaesthesist. 2003;52:1039–45.
53. Sreide E, Eriksson L, Hirlekar G, Eriksson H, Henneberg S, Sandin R, et al. Pre-operative fasting guidelines: an update. Acta Anaesthesiol Scand. 2005;49:1041–7.
54. Houser J. How many are enough? Statistical power analysis and sample size estimation in clinical research. J Clin Res Best Pract. 2007;3:1–5.